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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,187	07/30/2003	Jurgen Engel	103832-477-NP	9817

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EXAMINER
GEMBEH, SHIRLEY V

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
10/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/632,187	ENGEL ET AL.	
	Examiner	Art Unit	
	Shirley V. Gembeh	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/12/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed **7/12/07** presents remarks and arguments to the office action mailed **2/12/07**. Applicant's request for reconsideration of the rejection of claims in the last office action has been considered.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Statue of Claims

Claims 1-12 are pending in this office action. Claims 1-3, 5-6, 8-9 and 11-12 are currently amended.

Claim Rejections - 35 USC § 103

Claims 2, 7 and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al., 6,093,704, and Nickel et al., 6,696,428, and Nössner et al., 6,172,050 (all references already of record) in view of Calabresi et al., Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition as evident by Kasianenko 1998:87. (2pages) Abstract only.

Nickel et al. '704 teach anti-tumor compounds such as miltefosine or octadecyl (1,1-dimethylpiperidinio-4-yl) phosphate, wherein said compounds are used in pharmaceutical compositions or dose units (i.e. drug products) for effective treatment of cancer. Please see col.1, lines 10-17; col. 2, lines 40-44.

Nossner et al. disclose alkylphosphocholine compounds and their use in pharmaceutical compositions for treating tumors. The compounds are represented by the following General Formula (I).

Applicant argues again that the primary reference Nickel et al. for example, do not teach combination of an alkylphosphocholine with other chemotherapeutic drugs, and Calabresi et al. is drawn to a general teaching that combination of drugs are generally more effective.

In response, this is found unpersuasive for the reasons given below. An alkylphosphocholine has been used to treat cancer prior to Applicant discovery (see Kasianenko et al., where miltefosine is used in a treatment modality for skin lesions with breast cancer). The instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980), wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, given the teaching of the prior art methods of using an alkylphosphocholine and a chemotherapeutic agent individually for treating breast/mammary carcinoma, it would have

been obvious to use both compounds for the treatment of breast/mammary carcinoma because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as therapeutic agents.

Thus the argument is found unpersuasive and the rejection is maintained. The Kasianenko et al. reference is brought in as supportive evidence of a known fact in the prior art.

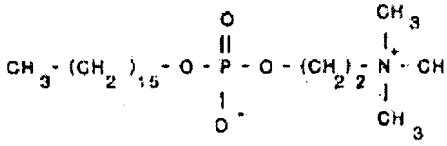
A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments filed have been fully considered but they are not persuasive. The reasons are set forth above and the rejection is maintained as in the last office action of record.

Claims 2, 7 and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hilgard et al., Cancer Chemother. Pharmcol., (1993) 32: 90-95 in view of Stekar et al., European J. of Cancer, Vol. 31(3), pp. 372-374, 1995 (Applicant submitted ref.).

Hilgard et al. teach compound of formula I



Miltefosine

wherein n is 2, m is 0, R is $C_1 - C_{20}$ as in the instant claim 1 (see page 91, lft. col.), for the treatment of mammary carcinoma, (see page 91 under Activity of miltefosine highlighted sec.), in combination with cisplatin (see page 93, highlighted sec.) as in claims 1-2, 5-6 and 9-12.

With regard to claim 2, R is $C_1 - C_{17}$ (see page 91, n is 2, X is O), wherein the alkylphosphocholine is in a carrier (see page 93,right column last line).

Stekar et al. teach the drug miltefosine is administered before or prior to the administration of cyclophosphamide (see page 373, rt. col.).

One of ordinary skill in the art would have been motivated to combine the above-cited references and administered miltefosine prior to administering the antitumor substance because the reference teaches so. Miltefosine, as taught above, has been used in combination therapy with other chemotherapeutic agents. One of ordinary skill in the art would have been motivated to use known antineoplastic agents an alkylphosphocholine and reasonably expect success in doing so because

cyclophosphamide conventionallyused in conjunction with other drugs for the treatment of cancer.

Thus, the claimed invention was prima facie obvious to make and use at the time it was made.

Applicant argues the claims 1-3, 5-6 and 8-12 have now been amended such that compound of Formula I (e.g. miltefosine) are no longer claimed as part of the combination therapy. These claims, as amended, only include combinations comprising cyclic alkylphosphocholines of Formula II in combination with an antitumor medication. Neither Hilgard or Stekar teach or suggest a method of treating mammary carcinoma with a combination of compounds of Formula II and an approved antitumor substance. Because the references in combination do not teach all of the limitations currently claimed, *a prima facie* case of obviousness has not been established.

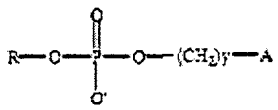
The rejection has been amended. Claims that include the ring structure have been withdrawn from the above rejection. Claims remain rejected now exclude the ring structure of Formula II. Applicant's amendment did not overcome the rejected claims.

As to Applicant's claim to synergism, the Patel et al. teach that when compounds of formula II are used with other chemotherapeutic agents, synergism is demonstrated.

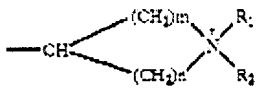
Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hilgard et al. Cancer Chemother. Pharmcol. (1993) 32: 90-95 taken with Stekar et al. European J. of Cancer Vol. 31(3) pp 372-374, 1995 in view of Nössner et al. US 6,172,050 further in view of Patel et al., Cancer research 62, 1401-1409, March 1, 2002.

Hilgard et al. and Stekar et al. are applied here as above.

Nössner et al., disclose alkylphosphocholine compounds and their use in pharmaceutical compositions for treating tumors, wherein the tumor is breast cancer (see col. 20, line 57). The compounds are represented by the following General



wherein A is the ring system



Formula (I): wherein the compound may be Octadecyl-1, 1-dimethylpiperidinio-4-yl phosphate (see col. 6, lines 45-50) as in instant claims 3 and 4. See col. 19, lines 34-45, where the above compound may be administered in a regimen. See lines 48-54, where a different agent from the above compound formula may be combined with cisplatin or, cyclophosphamide (see col. lines 50-51) in a pharmaceutically effective amount (see col. 20, lines 42-44) in a carrier or excipient (see same col.).

Cyclophosphamide is a heterocyclic compound and an antitumor agent/substance with low molecular weight, absent factual evidence. Therefore one of ordinary skill in the art would have been motivated to use these compounds with compounds of Fomulae I and II as required by instant claims 7-8.

One of ordinary skill would have been motivated to combine the above cited prior art to make and use the claimed invention at the time it was made. The prior art teaches the compounds of both instant formulae I and II have been used before the

claimed invention was made to treat breast cancer. Motivation is provided from the teachings of the prior art.

Thus, the claimed invention was prima facie obvious to make and use at the time it was made.

Applicant argues that the compounds of claims 1-3, 5-6 and 8-12 have been amended such that compounds formula I are no longer claimed. As taught by the prior art, Nössner et al. teach instant compound formula II. The ring structure in formula II is taught to further support previous the use of other chemotherapeutic agents.

Patel et al. Cancer research, at. Page 1401, teaches perifosine (a cyclic alkylphosphocholine) that has been used for the treatment of a mammary cancer. See underlining page. The reference further teaches alkylphosphocholine has synergistic cytotoxic properties with other chemotherapeutic agents, as cyclophosphamide or cisplatin. See underlining, page 1406. Thus one of ordinary skill in the art would have been motivated to use the claimed invention in view of Patel et al., because the prior art makes obvious the claimed invention.

As to Applicant's claim to synergism, the Patel et al. teach that when compounds of formula II are used with other chemotherapeutic agents, synergism is demonstrated.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SVG
9/22/07

Ardin H. Marschel 10/1/07
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SUPERVISORY PATENT EXAMINER